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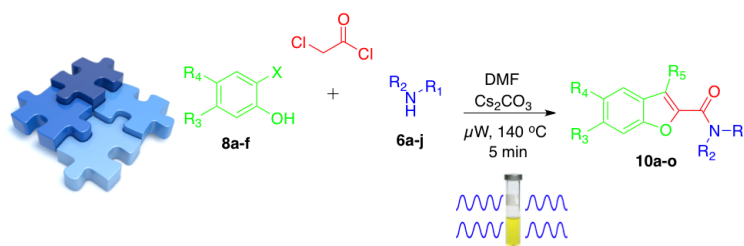
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A microwave-assisted multicomponent protocol for the synthesis of benzofuran-2-carboxamides

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ABSTRACT

A fast, versatile and practical microwave-assisted multicomponent protocol for the synthesis of substituted benzofuran-2-carboxamides has been developed. The present method proved to be effective on a series of commercially available amines, 2'-hydroxyacetophenones, aldehydes and benzonitriles and could be exploited in drug-discovery campaigns for the rapid identification of biologically active hit compounds.

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Introduction

The availability of rapid and versatile chemical approaches to produce highly functionalized molecules represents an essential medicinal chemistry tool for drug-discovery campaigns. Most of the new small molecule first-in-class drugs approved in the last 10 years came in fact from phenotypic screening of compounds' libraries rather than from targeted approaches.¹ The exploration of the chemical space around a privileged scaffold (privileged diversity-oriented synthesis; pDOS) is therefore considered an efficient strategy to increase the molecular diversity and discover new chemical probes for drug discovery.² Among the many privileged scaffold identified so far, benzofuran exhibits biological activity on a surprisingly high number of targets.³ It is present in numerous bioactive natural products, polymers and pharmaceuticals.⁴ Drugs containing benzofuran rings are in clinical use for the treatment of cardiac arrhythmias (Amiodarone, Dronedarone), urinary incontinence (Darifenacin), moderate Alzheimer disease (Galantamine), opioids overdose (Naloxone, Naltrexone), tuberculosis infections (Rifampicin, Rifapentin, Rifabutin), hypertension and heart failure (Saprisartan), jet-lag syndrome (Ramelteon).³ Benzofurans are reported active as plant growth regulators,⁵ insecticides,⁶ herbicides,⁷ anti-inflammatory,⁸ anticancer,⁹ antifungi,¹⁰ antibacterial,¹¹ antimalarial¹² and antiviral agents,¹³ MAO,¹⁴ TACE,¹⁵ aromatase,¹⁶ HDAC¹⁷ and GSK-3 inhibitors.¹⁸ Benzofuran represents also a privileged scaffold often found in

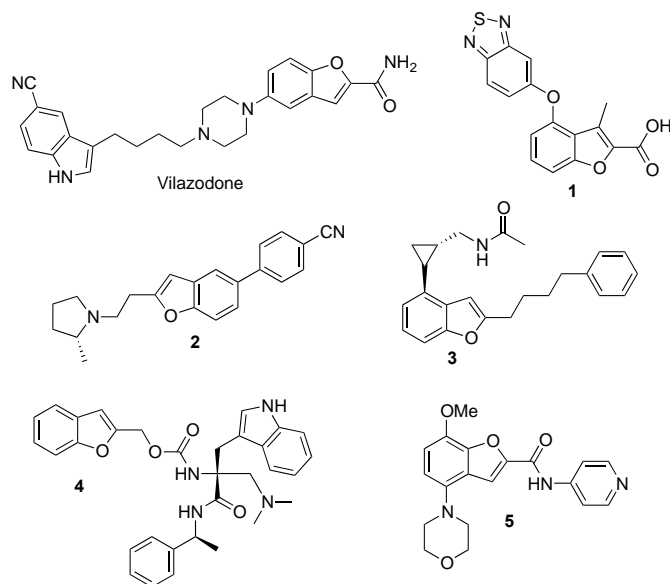
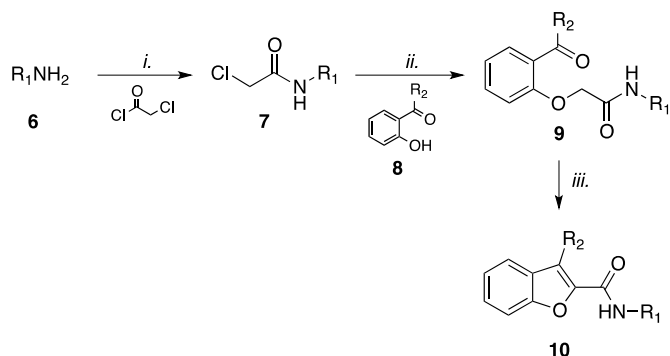


Figure 1. Representative benzofuran-based bioactive compounds

GPCRs-targeting ligands, like Vilazodone (5-HT_{1A} partial agonist) and antagonists on Endothelin (1),¹⁹ H₃ (2),²⁰ Melatonin (3),²¹ Neurokinin-1 (4)²² and Adenosine A_{2A} receptors (5)²³ (Figure 1). Due to the extraordinary wide range of possible

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applications it is not surprising that many efforts have been directed at the development of convenient synthetic strategies. Common synthetic approaches to substituted benzofurans include the modification of various arenes,^{4,23-25} with carbon-oxygen bond formation²⁶⁻²⁷ or through transition-metal catalysts.²⁸⁻³³ One of the most used synthetic strategies, is represented by a three step synthesis starting from amines **6** that are reacted with chloroacetyl chloride to give the chloroacetamide derivatives **7**, which are used in the O-alkylation of *o*-hydroxy aryl ketones to give the intermediates **9** that are finally cyclized to benzofurans **10**. (Scheme 1).³⁴

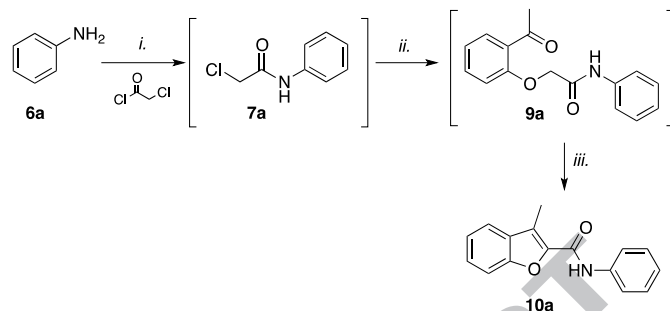


Scheme 1. Reagents and conditions: *i.* K₂CO₃, DCM, 0 °C-rt; *ii.* K₂CO₃, MeCN, reflux; *iii.* Cs₂CO₃, DMF, 110 °C.

These methodologies, although somehow valuable, normally require multiple steps/purification and are often affected by drawbacks such as long reaction times, low versatility due to limited availability of the starting materials and, in some cases, the need for expensive transition metal-containing reactants.^{25,26,29} Such characteristics are not particularly suitable for libraries generation in hit/drug discovery campaigns: the ideal synthetic approach should be fast, versatile, time and step economic and should be suitable, as far as possible, for combinatorial and parallel chemistry applications.³⁵ As a continuation of our interest in the development of microwave-assisted and multicomponent strategies for the synthesis of biologically active probes,³⁶⁻³⁸ we wanted to develop a new microwave-assisted procedure for the synthesis of substituted benzofurans in a one-pot fashion, since an efficient multicomponent approach to the synthesis of the benzofurans is still elusive. We report herein the first microwave-assisted one-pot three-component catalyst-free procedure for the synthesis of highly functionalized benzofuran-2-carboxamides directly from commercially available building blocks in extremely short reaction times.

Results and Discussion

As reported in Scheme 1, the standard conditions for the synthesis of α -halogen carboxamides normally requires that α -halogenacetyl chloride and an amine react in a polar aprotic solvent (like DMF) or in an apolar solvent in presence of a base (usually NEt₃) at room temperature for hours.³⁹⁻⁴³ We tried to speed up the synthesis of **7a** by microwave irradiation, heating **6a** and chloroacetyl chloride at 100 °C in DMF: after 5 minutes the reaction was completed and the resulting product **7a** was directly reacted with 2'-hydroxyacetophenone **8a** under the reaction conditions reported by Xie et al. (Scheme 2).⁴⁴ A complex reaction mixture was obtained and only traces of the product **10a** (3%) were isolated. Different reaction conditions were then tested to optimize the above protocol, changing the temperatures (50-150 °C), base (NEt₃) and solvents (dioxane, THF, EtOH, DMF), but they all gave a mixture with many decomposition products and a low amount of the desired compound **10a** (<5%).



Scheme 2. Reagents and conditions: *i.* DMF, μ W 100 °C, 5 min; *ii.* 2'-hydroxyacetophenone (**8a**), Cs₂CO₃, DMF, μ W 80 °C, 30 min; *iii.* Cs₂CO₃, DMF, μ W 140 °C, 30 min

At the end of the irradiation cycle, some unreacted 2'-hydroxyacetophenone **8a** was always detected. This, together with the hypothesized reaction mechanism (Figure 2) let us to speculate that the limiting step in the synthetic sequence was the O-alkylation. In order to speed-up this step, more reactive acetyl chlorides were tested (α -bromo- and α -iodoacetyl chlorides): also in this case, **10a** was formed only in traces (7 and 4 % respectively), probably because the more reactive α -bromo and α -iodo intermediates are also more prone to decomposition under our reaction conditions. The addition of a catalytic amount of iodide (in the form of KI or TBAI) to activate the α -chloroacetyl chloride,^{41-42,45} did not improve the yields of **10a**.

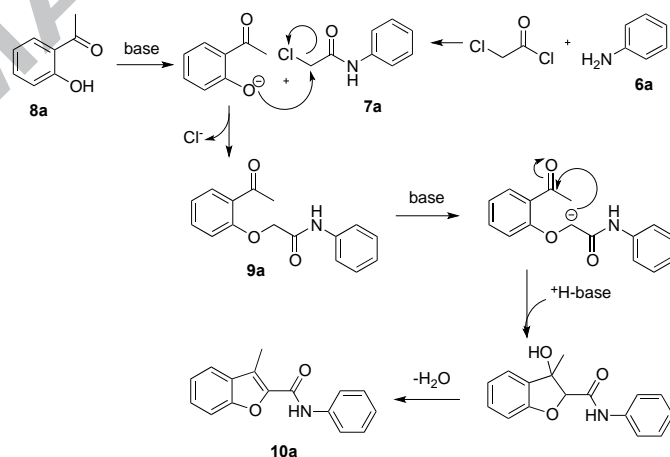
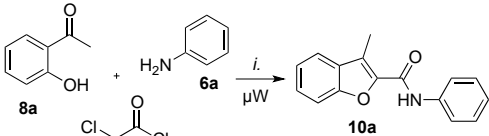


Figure 2. Hypothesized reaction mechanism.

As a practical observation, we noticed that at room temperature in dry DMF, without the addition of any base, the reaction between aniline **6a** and α -chloroacetyl chloride was occurring even in the presence of the 2'-hydroxyacetophenone. At this point, due to the high reactivity of the involved intermediates, we decided to combine all the building blocks (aniline, α -chloroacetyl chloride and 2'-hydroxyacetophenone) in a multicomponent fashion, using different solvents, bases, temperatures, and irradiation times (Table 1). As shown by the results summarized in Table 1, the desired benzofuran derivative **10a** was already obtained at 80 °C after 5 minutes of irradiation (Table 1, Entry 1) and its yield was increased with longer reactions times (Table 1, Entries 2-3). Higher reaction temperatures, up to 140 °C, allowed to reduce the irradiation time and also to increase the yields (Table 1, Entries 4-6). However, rising the temperature over 140 °C caused substantial decomposition and reduced yield of **10a** (Table 1, Entry 7). Using different solvents (EtOH, H₂O, THF, dioxane) (Table 1, Entry 9,10, 11, 12, 13) or a different base (K₂CO₃, Et₃N) (Table 1, Entry 8,10,14) caused a drastic drop in the yields.

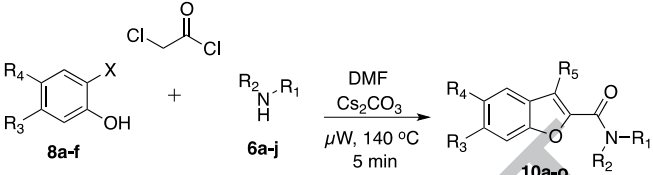
Table 1. Optimization of the multicomponent protocol



Entry	Solvent	Base	Temp (°C)	Time (min)	Yield (%) ^a
1	DMF	Cs ₂ CO ₃	80	5	16
2	DMF	Cs ₂ CO ₃	80	15	20
3	DMF	Cs ₂ CO ₃	80	30	32
4	DMF	Cs ₂ CO ₃	100	5	24
5	DMF	Cs ₂ CO ₃	120	5	35
6	DMF	Cs ₂ CO ₃	140	5	43
7	DMF	Cs ₂ CO ₃	160	5	15
8	DMF	K ₂ CO ₃	140	5	22
9	EtOH	Cs ₂ CO ₃	140	5	18
10	EtOH	K ₂ CO ₃	140	5	13
11	H ₂ O	Cs ₂ CO ₃	140	5	9
12	THF	Cs ₂ CO ₃	140	5	17
13	Dioxane	Cs ₂ CO ₃	140	5	15
14	DMF	NEt ₃	140	5	26

^aisolated yield

In summary, the optimal reaction conditions for the microwave-assisted multicomponent synthesis of benzofuran-2-carboxamides required the addition of anilines, α -chloroacetyl chloride and 2'-hydroxyacetophenones at 0 °C in dry DMF and subsequent irradiation at 140 °C for 5 minutes, in presence of Cs₂CO₃ as a base (Table 1, Entry 6). To verify the versatility and efficiency of the optimized microwave-assisted multicomponent protocol, a series of commercially available 2'-hydroxyacetophenones (**8a-d**) or benzaldehyde (**8e**) or benzonitrile (**8f**), α -chloroacetyl chloride and amines (**6a-j**) were used as building blocks to quickly generate a small collection of functionalized benzofuran-2-carboxamides **10a-o** (Table 2).

From the results reported in Table 2 it is possible to observe that electron-donating substituents on the *o*-hydroxyacetophenone ring (Entries 9-11) cause a drop of yield (products **10i-k**) compared to unsubstituted 2'-hydroxyacetophenones (Entry 1, product **10a**), probably because they deactivate the ketone moiety disfavoring the intramolecular cyclization. Salicylaldehyde (**8e**) or 2-hydroxybenzonitrile (**8f**) can also be used in place of 2'-hydroxyacetophenones **8a-d**, giving benzofuran-2-carboxamides (**10n,o**; Entries 14-15) with a different substituent in position C3 (R₅ = H, NH₂). Strong *para* electron-withdrawing groups on the aniline (Entries 4,6) led to low yields of the corresponding benzofurans **10d,f**: this effect is probably due to a competing deprotonation of the NH-proton rather than the α -position of the amide intermediate **9** before heterocyclization. Mild *para* electron-donating substituents on the aniline slightly increase the reaction yields (Entry 5), while *meta* electron-withdrawing groups cause a drop in the yields (Entries 7-8). Strong electron-donating substituents cause an increase in the yields (Entry 12). Secondary amines are also well tolerated and gave the corresponding benzofuran-2-carboxamides in good yields (Entry 2). Aliphatic amines (e.g. morpholine) also gave the desired product **10m** after a little longer reaction time (Entry 13).

Table 2. Microwave-assisted multicomponent synthesis of benzofuran-2-carboxamides **10a-o**


Entry	Cpds	R ₁	R ₂	R ₃	R ₄	R ₅	Yield (%) ^a
1	10a	Ph	H	H	H	Me	43
2	10b	Ph	Ph	H	H	Me	45
3	10c	4-ClPh	H	H	H	Me	59
4	10d	4-NO ₂ Ph	H	H	H	Me	25
5	10e	4- <i>i</i> -PrPh	H	H	H	Me	44
6	10f	4-CF ₃ Ph	H	H	H	Me	27
7	10g	3-FPh	H	H	H	Me	20
8	10h	3-ClPh	H	H	H	Me	25
9	10i	Ph	H	Me	H	Me	18
10	10j	Ph	H	OMe	H	Me	15
11	10k	Ph	H	H	OMe	Me	19
12	10l	3-OMePh	H	H	H	Me	51
13	10m			H	H	Me	35 ^b
14	10n	Ph	H	H	H	H	38
15	10o	Ph	H	H	H	NH ₂	33

^aisolated yield after flash chromatography; ^breaction time :10 minutes

Conclusions

In conclusion we have developed a practical, versatile, fast and transition metal-free microwave-assisted multicomponent procedure for the synthesis of benzofuran-2-carboxamides starting from commercially available and cheap building blocks. This methodology allowed us to generate highly functionalized 3-alkylbenzofurans (Entries 1-13), 3-aminobenzofurans (Entry 15) and 3-unsubstituted benzofurans (Entry 14) in a short reaction time and acceptable yields. Further exploitation of the approach herein reported may allow to quickly generate libraries of substituted benzofurans for drug-discovery campaigns.

Acknowledgment

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Supplementary Material

Supplementary data (synthetic procedures, ¹H and ¹³C NMR spectra) associated with this article can be found, in the online version, at

References and notes

- Eder, J.; Sedrani, R.; Wiesmann, C. *Nature Rev. Drug Discov.* **2014**, *13*, 577-587.
- Oh, S.; Park, S. B. *Chem. Comm.* **2011**, *47*, 12754-12761.
- Nevagi, R. J.; Dighe, S. N.; Dighe, S. N. *Eur. J. Med. Chem.* **2015**, *97*, 561-581.
- De Luca, L.; Nieddu, G.; Porcheddu, A.; Giacomelli, G. *Curr. Med. Chem.* **2009**, *16*, 1-20.
- Rentzea, C.; Reissenweber, G.; Feuerherd, K. H.; Jung, J. *Ger. Pat. Offen.* **1983**, *3*, 139250.
- Jacobsen, M.; Crosby, D. G. *Natural Occuring Insecticides*, Dekker: New York, New York, 1971.
- Sasaki, N.; Kudo, S.; Endo, K.; Suzuki, R. *Chem Abstr.* **1992**, *117*, 178993v.
- Xie, Y. S.; Kumar, D.; Bodduri, V. D. V.; Tarani, P. S.; Zhao, B. X.; Miao, J. Y.; Jang, K.; Shin, D. S. *Tetrahedron Lett.* **2014**, *55*, 2796-2800.
- Flynn, B. L.; Hamel, E.; Jung, M. K. *J. Med. Chem.* **2002**, *45*, 2670-2673.
- Telvekar, V. N.; Belubbi, A.; Bairwa, V. K.; Satardekar, K. *Bioorg. Med. Chem. Lett.* **2012**, *6*, 2343-2346.
- Bandgar, B. P.; Patil, S. A.; Korbadi, B. L.; Biradar, S. C.; Nile, S. N.; Khobragade, C. N. *Eur. J. Med. Chem.* **2010**, *45*, 3223-3227.
- Yu, Z. Y.; Brannigan, J. A.; Moss, D. K.; Brzozowski, A. M.; Wilkinson, A. J.; Holder, A. A.; Tate, E. W.; Leatherbarrow, R. J. *J. Med. Chem.* **2012**, *55*, 8879-8890.
- Whitby, L. R.; Lee, A. M.; Kunz, S.; Oldstone, M. B. A.; Boger, D. L. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3771-3774.
- Pisani, L.; Barletta, M.; Soto-Otero, R.; Nicolotti, O.; Mendez-Alvarez, E.; Catto, M.; Introcaso, A.; Stefanachi, A.; Cellamare, S.; Altomare, C.; Carotti, J. *Med. Chem.* **2013**, *56*, 2651-2664.
- Lu, Z.; Ott, G. R.; Anand, R.; Liu, R. Q.; Covington, M. B.; Vaddi, K.; Qian, M.; Newton, R. C.; Christ, D. D.; Trzaskos, J.; James, J.; Duan, W. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1958-1962.
- Saberi, M. R.; Vinh, T. K.; Yee, S. W.; Griffiths, B. J. N.; Evans, P. J.; Simons, C. *J. Med. Chem.* **2006**, *49*, 1016-1022.
- Varasi, M.; Thaler, F.; Abate, A.; Bigogno, C.; Boggio, R.; Carenzi, G.; Cataudella, T.; Dal Zuffo, R.; Fulco, M. C.; Rozio, M. G.; Mai, A.; Dondio, G.; Minucci, S.; Mercurio, C. *J. Med. Chem.* **2011**, *54*, 3051-3064.
- Gaisina, I. N.; Gallier, F.; Ougolkov, A. V.; Kim, K. H.; Kurome, T.; Guo, S.; Holzle, D.; Luchini, D. N.; Blond, S. Y.; Billadeau, D. D.; Kozikowski, A. P. *J. Med. Chem.* **2009**, *52*, 1853-1863.
- Cai, J.; Chen, J.; Cao, M.; Wang, P.; Feng, C.; Ji, M. *Med. Chem. Res.* **2013**, *22*, 5472-5480.
- Cowart, M.; Faghih, R.; Curtis, M. P.; Gfesser, G. A.; Bennani, Y. L.; Black, L. A.; Pan, L.; Marsh, K. C.; Sullivan, J. P.; Esbenshade, T. A.; Fox, G. B.; Hancock, A. A. *J. Med. Chem.* **2005**, *48*, 38-55.
- Sun, L. Q.; Takaki, K.; Chwn, J.; Iben, L.; Knipe, J. O.; Pajor, L.; Mahle, C. D.; Ryan, E.; Xu, C. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5157-5160.
- Ashwood, V. A.; Field, M. J.; Horwell, D. C.; Julien-Larose, C.; Lewthwaite, R. A.; McCleary, S.; Pritchard, M. C.; Raphy, J.; Singh, L. *J. Med. Chem.* **2001**, *44*, 2276-2285.
- Saku, O.; Saki, M.; Kurokawa, M.; Ikeda, K.; Uchida, S. I.; Takizawa, T.; Uesaka, N. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3768-3771.
- Yamashita, A.; Toy, A.; Scallill, T. *J. Org. Chem.* **1989**, *54*, 3625-3634.
- Sakamoto, T.; Kondo, Y.; Yasuhara, A.; Yamanaka, H. *Tetrahedron* **1991**, *47*, 1877-1886.
- Willis, M. C.; Taylor, D.; Gillmore, A. T. *Org. Lett.* **2004**, *6*, 4755-4757.
- Anderson, K. W.; Ikawa, T.; Tundel, R. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 10964-10965.
- Cho, C. H.; Neuenswander, B.; Lushington, G. H.; Larock, R. C. *J. Comb. Chem.* **2008**, *10*, 941-947.
- Gabriele, B.; Mancuso, R.; Salerno, G.; Costa, M. *J. Org. Chem.* **2007**, *72*, 9278-9282.
- Nagamochi, M.; Fang, Y. Q.; Lautens, M. *Org. Lett.* **2007**, *9*, 2955-2958.
- Bernini, R.; Cacchi, S.; De Salve, I.; Fabrizi, G. *Synthesis* **2007**, *6*, 873-882.
- Watanabe, M.; Yamamoto, T.; Nishiyama, M. *Angew. Chem. Int. Ed.* **2000**, *39*, 2501-2504.
- Ackermann, L.; Kaspar, L. T. *J. Org. Chem.* **2007**, *72*, 6149-6153.
- Xia, S.; Wang, X. H.; Liu, J. Q.; Liu, C.; Chen, J. B.; Zoo, H.; Xie, Y. S.; Dong, W. L.; Shin, D. S. *B. Korean Chem. Soc.* **2014**, *35*, 1743-1748.
- Greysen, H. M.; Schoenen, F.; Wagner, D.; Wagner, R.; Wagner, R. *Nat. Rev. Drug Discov.* **2003**, *2*, 222-230.
- Tassini, S.; Castagnolo, D.; Scalacci, N.; Kissova, M.; Armijos-Rivera, J. I.; Giagnorio, F.; Maga, G.; Costantino, G.; Crespan, E.; Radi, M. *MedChemComm* **2016**, DOI: 10.1039/C5MD00462D.
- Vincetti, P.; Caporuscio, F.; Kaptein, S.; Gioiello, A.; Mancino, V.; Suzuki, Y.; Yamamoto, N.; Crespan, E.; Lossani, A.; Maga, G.; Rastelli, G.; Castagnolo, D.; Neyts, J.; Leyssen, P.; Costantino, G.; Radi, M. *J. Med. Chem.* **2015**, *58*, 4964-4975.
- Radi, M.; Vallerini, G. P.; Petrelli, A.; Vincetti, P.; Costantino, G. *Tetrahedron Lett.* **2013**, *54*, 6905-6908.
- Kumar, B. R. P.; Baig, N. R.; Sudhir, S.; Kar, K.; Kiranmai, M.; Pankaj, M.; Joghee, N. M. *Bioorg. Chem.* **2012**, *45*, 12-28.
- Guo, X.; Ma, X.; Yang, Q.; Xu, J.; Huang, L.; Jia, J.; Shou, J.; Liu, L.; Chen, W.; Chu, H.; Wei, J.; Zhang, X.; Sun, H.; Tang, Y.; You, Q. *Eur. J. Med. Chem.* **2014**, *81*, 89-94.
- Kobayashi-Matsunaga, Y.; Ishii, T.; Hamaguchi, T.; Osada, H.; Sato, M. *Lett. Drug Des. Discov.* **2005**, *2*, 224-227.
- Ma, L.; Li, S.; Zhang, H.; Chen, J.; Liu, L.; Ye, X.; Chen, Z.; Xu, Q.; Chen, T.; Yang, J.; Qiu, N.; Wang, G.; Peng, A.; Ding, Y.; Wei, Y.; Chen, L. *Eur. J. Med. Chem.* **2011**, *46*, 2003-2010.
- Ma, L.; Xie, C.; Ma, Y.; Liu, J.; Xiang, M.; Ye, X.; Zheng, H.; Chen, Z.; Xu, Q.; Chen, T.; Chen, J.; Yang, J.; Qiu, N.; Wang, G.; Liang, X.; Peng, A.; Yang, S.; Wei, Y.; Chen, L. *J. Med. Chem.* **2011**, *54*, 2060-2068.
- Xie, Y. S.; Kumar, D.; Bodduri, V. D.; Tarani, P. S.; Zhao, B. X.; Miao, J. Y.; Jang, K.; Shin, D. S. *Tetrahedron Lett.* **2014**, *55*, 2796-2800.
- Perez, M.; Ayerbe, N.; Fourier, C.; Sigogneau, I.; Pauwels, P. J.; Palmier, C.; John, G. W.; Valentiu, J. P.; Halazy, S. *Eur. J. Med. Chem.* **1997**, *32*, 129-134.

Highlights

- Microwave-assisted synthesis of highly functionalized benzofuran-2-carboxamides.
- Compounds are obtained in a one-pot multicomponent reaction after 5 minutes.
- A simple and versatile metal-free approach incorporating commercial synthons.